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L11	l10 and (cancer$ or tumor$)	47	L11
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L6	L4 and STAT	1	L6
L5	L4 and STAT3	0	L5
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DB=USPT; PLUR=YES; OP=OR			
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Granulocyte colony-stimulating factor activation of Stat3 alpha and Stat3 beta in immature normal and leukemic human myeloid cells.

Chakraborty A, White SM, Schaefer TS, Ball ED, Dyer KF, Tweardy DJ.

Department of Medicine, University of Pittsburgh School of Medicine, PA, USA.

Granulocyte colony-stimulating factor (G-CSF) is the cytokine critica for directing neutrophilic granulocyte differentiation. Acute myelogenous leukemia (AML) cells, which frequently arise from this lineage, respond aberrantly to G-CSF by proliferating without differentiating. The basis for this abnormal responses is unknown. In the present study, we investigated whether G-CSF signaling in immature normal and leukemic human myeloid cells diverges at the level of activation of signal transducers and activators of transcription (STAT) proteins. We compared the profile of STAT proteins activated in G-CSF-stimulated immature normal and leukemic human myeloid cells. G-CSF activated Stat3 alpha in all AML cell lines examined except HL60 and in three of six uncultured AML patient samples. In normal human CD34+ bone marrow cells and HL60 cells, both reported to differentiate in response to G-CSF, G-CSF did not activate Stat3 alpha; rather, it activated only an 83 kD form of Stat3 that proved to be the human homologue of a short form of Stat3, Stat3 beta. Because the transcriptional activity of Stat3 beta is distinct from Stat3 alpha, these results suggest that the balance of the two Stat3 isoforms in myeloid cells may influence the cellular pattern of gene activation and consequently the ability of these cells to differentiate in

response to G-CSF.

PMID: 8839834 [PubMed - indexed for MEDLINE]

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L3 ANSWER 1 OF 34 MEDLINE
ACCESSION NUMBER: 1999111028 MEDLINE
DOCUMENT NUMBER: 99111028 PubMed ID: 9815779
TITLE: Blockade of mitogen-activated protein kinase cascade signaling in interleukin 6-independent multiple myeloma cells.
AUTHOR: Ogata A; Chauhan D; Urashima M; Teoh G; Treon S P; Anderson K C
CORPORATE SOURCE: Division of Hematologic Malignancies, Dana-Farber Cancer Institute, and Department of Medicine, Harvard Medical School, Boston, Massachusetts 02215, USA.
CONTRACT NUMBER: CA 50947 (NCI)
SOURCE: CLINICAL CANCER RESEARCH, **(1997 Jun)** 3 (6) 1017-22.
Journal code: C2H; 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

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NEWS 14	Dec 10	WPINDEX/WPIDS/WPIX New and Revised Manual Codes for 2002
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NEWS 16	Dec 17	WELDASEARCH now available on STN
NEWS 17	Dec 17	STANDARDS now available on STN
NEWS 18	Dec 17	New fields for DPCI
NEWS 19	Dec 19	CAS Roles modified
NEWS 20	Dec 19	1907-1946 data and page images added to CA and CAplus
NEWS 21	Jan 25	BLAST(R) searching in REGISTRY available in STN on the Web
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LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990301
Last Updated on STN: 20000303
Entered Medline: 19990212

AB Interleukin 6 (IL-6) is a growth factor for multiple myeloma (MM) cells, yet not all MM cell lines or **patient** cells require IL-6 for their growth. It is well known that IL-6 activates the signal transducers and activators of transcription (stat) 1-**stat3** heterodimer, **stat3** homodimer, and Ras-dependent mitogen-activated protein kinase (MAPK) cascades in multiple cell systems. We have shown previously that the MAPK pathway is an important pathway for IL-6-mediated MM cell growth. In this study, we delineate the pattern of upstream MAPK cascade activation in IL-6-responsive B9 cells and in IL-6-nonresponsive U266, OCI-My5, and RPMI8226 MM cells to define sites of blockade of this pathway associated with loss of responsiveness to IL-6. In B9 cells, IL-6 triggered the following in sequence: gp130 phosphorylation, gp130-to-protein tyrosine phosphatase 1D (PTP1D) binding, PTP1D phosphorylation, PTP1D complex formation with Grb2-Son of sevenless 1 (Sos1), and Sos1 phosphorylation. gp130 phosphorylation, gp130-to-PTP1D binding, PTP1D phosphorylation, and PTP1D-to-Grb2 binding are also induced by IL-6 in all IL-6-independent MM cell lines studied. However, Grb2 is not associated with Sos1, and neither Grb2-to-Sos1 binding nor Sos1 phosphorylation is triggered by IL-6 in OCI-My5 MM cells. On the other hand, Grb2 and Sos1 are associated constitutively in U266 and RPMI8226 MM cells, but phosphorylation of Sos1 is not induced by IL-6. These data suggest that lack of Sos1 activation is associated with loss of IL-6 responsiveness in MM cell lines that grow independently of IL-6.

L3 ANSWER 2 OF 34 MEDLINE
ACCESSION NUMBER: 1999061782 MEDLINE
DOCUMENT NUMBER: 99061782 PubMed ID: 9845531
TITLE: Thrombopoietin induces association of Crkl with STAT5 but not **STAT3** in human platelets.
AUTHOR: Ozaki K; Oda A; Wakao H; Rhodes J; Druker B J; Ishida A; Wakui M; Okamoto S; Morita K; Handa M; Komatsu N; Ohashi H; Miyajima A; Ikeda Y
CORPORATE SOURCE: Division of Hematology, Department of Internal Medicine, and Blood Center, Keio University, Tokyo, Japan.
SOURCE: BLOOD, **(1998 Dec 15)** 92 (12) 4652-62.
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990205

AB Crkl, a 39-kD SH2, SH3 domain-containing adapter protein, is constitutively tyrosine phosphorylated in hematopoietic cells from chronic myelogenous leukemia (CML) **patients**. We recently reported that thrombopoietin induces tyrosine phosphorylation of Crkl in normal platelets. In this study, we demonstrate that thrombopoietin induces association of Crkl with a tyrosine phosphorylated 95- to 100-kD protein

in platelets and in UT7/TPO cells, a thrombopoietin-dependent megakaryocytic cell line. With specific antibodies against STAT5, we demonstrate that the 95- to 100-kD protein in Crkl immunoprecipitates is STAT5. This coimmunoprecipitation was specific in that Crkl immunoprecipitates do not contain **STAT3**, although **STAT3** becomes tyrosine phosphorylated in thrombopoietin-stimulated platelets. The coimmunoprecipitaion of Crkl with STAT5 was inhibited by the immunizing peptide for Crkl antisera or phenyl phosphate (20 mmol/L). After denaturing of Crkl immunoprecipitates, Crkl was still immunoprecipitated by Crkl antisera. However, coimmunoprecipitation of STAT5 was not observed. Coincident with STAT5 tyrosine phosphorylation, thrombopoietin induces activation of STAT5 DNA-binding activity as demonstrated by electrophoretic mobility shift assays (EMSA). Using a beta-casein promoter STAT5 binding site as a probe, we have also demonstrated that Crkl antisera supershift the STAT5-DNA complex, suggesting that Crkl is a component of the complex in the nucleus. Furthermore, interleukin-3 (IL-3), granulocyte-macrophage colony-stimulating factor (GM-CSF), and erythropoietin also induce Crkl-STAT5 complex formation in responding cells in a stimulation-dependent manner. In vitro, glutathione S-transferase (GST)-Crkl bound to STAT5 inducibly through its SH2 domain. These results indicate that thrombopoietin, IL-3, GM-CSF, and erythropoietin commonly induce association of STAT5 and Crkl and that the complex translocates to the nucleus and binds to DNA. Interestingly, such association between STAT5 and Crkl was not observed in cytokine-stimulated murine cells, suggesting an intriguing possibility that components of the human STAT5-DNA complex may be different from those of the murine counterpart.

L3 ANSWER 3 OF 34 MEDLINE
ACCESSION NUMBER: 1998414257 MEDLINE
DOCUMENT NUMBER: 98414257 PubMed ID: 9743325
TITLE: IFN-alpha is a survival factor for human myeloma cells and reduces dexamethasone-induced apoptosis.
AUTHOR: Ferlin-Bezombes M; Jourdan M; Liautard J; Brochier J; Rossi J F; Klein B
CORPORATE SOURCE: Institut National de la Sante et de la Recherche Medicale, Unit 475, Montpellier, France.
SOURCE: JOURNAL OF IMMUNOLOGY, **(1998 Sep 15)** 161 (6) 2692-9.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981020
Last Updated on STN: 19981020
Entered Medline: 19981006

AB IFN-alpha is used as a maintenance therapy in **patients** with multiple myeloma, but its benefit is a matter of controversy. In vitro studies show that IFN-alpha can both stimulate and inhibit myeloma cell proliferation. We have tested the effect of IFN-alpha on the survival of myeloma cell lines and primary plasma cells. IFN-alpha significantly reduced the apoptosis induced by removal of IL-6 in four IL-6-dependent myeloma cell lines. It also reduced the level of apoptosis induced by dexamethasone in these cell lines as well as in purified primary myeloma cells from seven **patients**. IFN-alpha promoted the survival of myeloma cells, which, following removal of IL-6, were blocked in G1 and died. However, unlike IL-6, IFN-alpha-treated cells remained mainly

blocked in the G1 phase of the cycle. While the effects of IL-6 are mediated through stimulation of its gp130 receptor subunit, the IFN-alpha-induced survival of myeloma cells was independent of gp130 transducer activation (as demonstrated using a neutralizing anti-gp130 Ab). However, the signal transduction cascades activated by these two cytokines share at least some common elements, since stimulation with either IFN-alpha or IL-6 resulted in **STAT3** phosphorylation. These results indicate that IFN-alpha promotes the survival, but not the proliferation, of myeloma cells, preventing the apoptosis induced by removal of IL-6 or addition of dexamethasone. This survival factor activity may explain the conflicting reports on the effects of IFN-alpha on myeloma cell proliferation.

L3 ANSWER 4 OF 34 MEDLINE
ACCESSION NUMBER: 1998361782 MEDLINE
DOCUMENT NUMBER: 98361782 PubMed ID: 9694725
TITLE: Differential binding activity of the transcription factor LIL-STAT in immature and differentiated normal and leukemic myeloid cells.
AUTHOR: Tuyt L M; Bregman K; Lummen C; Dokter W H; Vellenga E
CORPORATE SOURCE: Division of Hematology and Center for Biomedical Technology, University of Groningen, The Netherlands.
SOURCE: BLOOD, **(1998 Aug 15)** 92 (4) 1364-73.
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980910

AB Cytokines and growth factors induce activation of the family of signal transducers and activators of transcription (Stats) that directly activate gene expression. Recently, constitutively activated Stat1, **Stat3**, and Stat5 were identified in nuclear extracts of acute myeloid leukemia (AML) **patients**, suggesting involvement of constitutive Stat activity in the events of leukemogenesis. In the present study, blasts of nine AML cases were investigated for the constitutive binding activity of the recently identified transcription factor LIL-Stat (LPS- and IL-1-inducible Stat). Band-shift assays were performed using the LPS-and IL-1-responsive element (LILRE) oligonucleotide, a gamma interferon activation site-like site that is present in the human IL-1beta promoter. Constitutive LIL-Stat binding activity was observed in three leukemic cell lines and in seven out of nine AML cases. Transient transfection studies with a reporter plasmid containing three sequential LIL-Stat binding sites showed distinct transcriptional activity of LIL-Stat only in those AML blasts that constitutively expressed LIL-Stat. In CD34+ cells LIL-Stat also constitutively bound to its consensus sequence. However, when these cells were cultured in the presence of macrophage-colony stimulating factor (M-CSF) and stem cell factor (SCF) for differentiation along the monocytic lineage, the LIL-Stat binding activity disappeared totally. In agreement with these findings neither mature monocytes nor granulocytes showed constitutive or inducible LIL-Stat binding activity. We conclude that the LIL-Stat transcription factor is constitutively activated in undifferentiated and leukemic hematopoietic cells, but not in mature

cells. This may suggest a role for this transcription factor in the process of differentiation.
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L3 ANSWER 5 OF 34 MEDLINE
ACCESSION NUMBER: 1998343580 MEDLINE
DOCUMENT NUMBER: 98343580 PubMed ID: 9679986
TITLE: Expression of signal transducers and activators of transcription proteins in acute myeloid leukemia blasts.
AUTHOR: Xia Z; Baer M R; Block A W; Baumann H; Wetzler M
CORPORATE SOURCE: Department of Hematologic Oncology, Roswell Park Cancer Institute, Buffalo, New York 14263, USA.
CONTRACT NUMBER: CA16056 (NCI)
CA26122 (NCI)
SOURCE: CANCER RESEARCH, **(1998 Jul 15)** 58 (14) 3173-80.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980820
Last Updated on STN: 19980820
Entered Medline: 19980807

AB Hematopoietic cytokine receptor signaling pathways involve activation of signal transducers and activators of transcription (STAT) proteins, which are postulated to be involved in cellular differentiation. Aberrant STAT isoforms (beta forms rather than the normal alpha forms) have been described and have been found to block the normal signaling pathway from the receptor. Bcr/Abl proteins have been suggested to directly activate STATs, without exposure to growth factors. We asked whether STATs play a role in leukemogenesis. We analyzed constitutive and induced patterns of STAT activity in pretreatment blasts from 36 newly diagnosed acute myeloid leukemia (AML) **patients** and studied protein tyrosine kinases (PTKs) that may be involved in STAT activity, using in vitro and in-gel kinase assays. The beta forms were expressed in 21 of 27 samples (78%). Constitutive **STAT3** and STAT5 activity was found in samples from 28 and 22% of **patients**, respectively. Response to exogenous cytokines identified two groups. STAT activity in one group was modulated by exogenous cytokines: constitutive STAT activity increased in some **patients** but decreased or disappeared in response to cytokines in others. The second group was cytokine insensitive. Additionally, we found constitutive PTK activity in two **patients** whose blasts demonstrated constitutive STAT activity, suggesting that PTKs use cytokine receptor signal pathways to activate STATs in AML blasts without exposure to exogenous cytokines. Our data suggest that (a) constitutive expression of aberrant STATs may be involved in blocking differentiation of AML blasts, (b) exogenous cytokines may activate STAT-inhibitory pathways, and (c) STATs may be activated by PTKs in some AML blasts.

L3 ANSWER 6 OF 34 MEDLINE
ACCESSION NUMBER: 1998240989 MEDLINE
DOCUMENT NUMBER: 98240989 PubMed ID: 9581833
TITLE: Prolactin activates Stat1 but does not antagonize Stat1 activation and growth inhibition by type I interferons in human breast cancer cells.
AUTHOR: Schaber J D; Fang H; Xu J; Grimley P M; Rui H

CORPORATE SOURCE: Department of Pathology, Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814, USA.
CONTRACT NUMBER: RO1 DK52013-01A1 (NIDDK)
SOURCE: CANCER RESEARCH, **(1998 May 1)** 58 (9) 1914-9.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980611
Last Updated on STN: 19980611
Entered Medline: 19980602

AB Type I interferons (IFN alpha and IFN beta) are presently used in the adjuvant treatment of several human cancers. However, these cytokines have demonstrated only modest success in breast cancer therapy, and research efforts have focused on improving their efficacy. Recent progress in understanding the molecular mechanisms underlying the antiproliferative effects of IFNs has identified the cytoplasmic transcription factor Stat1 as a critical mediator. It is, therefore, possible that IFN-induced growth inhibition of mammary epithelial cells is counteracted by other cytokines that also use Stat1. One such candidate IFN-antagonist with particular relevance to breast cancer is the mammotropic hormone prolactin (PRL). The main goal of this study was to examine whether PRL would interfere with type I IFN (IFN alpha/beta) signal transduction by competing for limited cytoplasmic Stat factors. A second aim was to test whether pretreatment of mammary tumor cell lines with IFN gamma could enhance the effect of IFN alpha/beta. By analyzing the effect of PRL on IFN alpha/beta-induced tyrosine phosphorylation of Stat proteins and their binding to IFN-regulated genes, we now report that costimulation of PRL receptors did not interfere with IFN alpha/beta signals in several human breast cancer cell lines, including T47D, MCF-7, and BT-20. Specifically, PRL did not affect IFN alpha/beta-induced tyrosine phosphorylation or heterodimerization of Stat1 and Stat2 in any cell line. Instead, IFN alpha/beta- and PRL-induced tyrosine phosphorylation of Stat1 was additive and occurred without evidence of competition for limited concentrations of cytoplasmic Stat1. A similar additive relationship was observed on IFN alpha/beta- and PRL-induced **Stat3** tyrosine phosphorylation. Furthermore, electrophoretic mobility shift assays showed that type I IFNs induced predominantly Stat1-Stat2 or Stat1-**Stat3** heteromeric complexes with various IFN-response elements of IFN-stimulated genes, whereas PRL induced Stat1 homodimers. Despite significant mutual use of Stats by IFNs and PRL, these results indicated a high degree of signaling specificity in the two receptor systems, and that cytoplasmic levels of Stat proteins were not limiting. Similarly, PRL did not interfere with the growth-inhibitory effect of IFN beta. On the other hand, the study indicated that pretreatment of human breast cancer cell lines with IFN gamma enhanced the growth-inhibitory action of type I IFNs, suggesting a possible avenue for improving the effect of type I IFNs in the treatment of breast cancer **patients**.

L3 ANSWER 7 OF 34 MEDLINE
ACCESSION NUMBER: 1998158472 MEDLINE
DOCUMENT NUMBER: 98158472 PubMed ID: 9498707
TITLE: Activated Stat related transcription factors in acute leukemia.
AUTHOR: Gouilleux-Gruart V; Debierre-Grockiego F; Gouilleux F; Capiod J C; Claisse J F; Delobel J; Prin L
CORPORATE SOURCE: Laboratoire d' Immunologie and Laboratoire d' Hematologie, Centre Hospitalier Universitaire d'Amiens, France.
SOURCE: LEUKEMIA AND LYMPHOMA, **(1997 Dec)** 28 (1-2) 83-8.
Ref: 48
Journal code: BNQ; 9007422. ISSN: 1042-8194.
PUB. COUNTRY: Switzerland
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980422
Last Updated on STN: 19980422
Entered Medline: 19980414

AB Cell proliferation and differentiation are under the control of cytokines and growth factors. Different signaling pathways are involved in the transmission of a specific signal through successive phosphorylation and dephosphorylation of proteins leading to gene transcription necessary for growth and differentiation. The cytokines and growth factors activate the Stat family of transcription factors. The Jak-Stat pathway is essential for cytokine signal transduction. Dysregulation of this cascade might lead to uncontrolled hematopoiesis. Studies have been carried out to examine the functionality of this pathway in cells from **patients** with acute leukemia. Members of the Stat protein family (Stat1, **Stat3** and Stat5) are constitutively activated in cells collected from some acute leukemias suggesting dysregulation of the Jak-Stat pathway. Evidence of the existence of constitutively activated spliced variants of **Stat3** and Stat5 proteins are described. The mechanisms of such activation remain to be clarified.

L3 ANSWER 8 OF 34 MEDLINE
ACCESSION NUMBER: 1998064072 MEDLINE
DOCUMENT NUMBER: 98064072 PubMed ID: 9399961
TITLE: B lymphocytes from **patients** with chronic lymphocytic leukemia contain signal transducer and activator of transcription (STAT) 1 and **STAT3** constitutively phosphorylated on serine residues.
AUTHOR: Frank D A; Mahajan S; Ritz J
CORPORATE SOURCE: Department of Adult Oncology, Dana-Farber Cancer Institute,
Boston, Massachusetts 02115, USA..
david_frank@dfci.harvard.edu
CONTRACT NUMBER: CA-41619 (NCI)
CA-66966 (NCI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, **(1997 Dec 15)** 100 (12) 3140-8.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980206
Last Updated on STN: 19980206
Entered Medline: 19980126

AB To explore the pathogenesis of chronic lymphocytic leukemia (CLL), we examined whether phosphorylation of one or more signal transducer and activator of transcription (STAT) factors was abnormal in cells from CLL **patients**. No constitutive tyrosine phosphorylation was detected on any STAT in CLL cells. To assess the phosphorylation of serine residues of STAT1 and **STAT3** in CLL cells, we raised antibodies that specifically recognize the form of STAT1 phosphorylated on ser-727 and the form of **STAT3** phosphorylated on ser-727. We found that in 100% of **patients** with CLL (n = 32), STAT1 and **STAT3** were constitutively phosphorylated on serine. This was in contrast to normal peripheral blood B lymphocytes or CD5+) B cells isolated from tonsils, in which this phosphorylation was absent. Serine phosphorylation of STAT1 and **STAT3** was seen occasionally in other leukemias, but it was a universal finding only in CLL. The serine phosphorylation of these STATs was a continuous process, as incubation of CLL cells with the kinase inhibitor H7 led to the dephosphorylation of these serine residues. The STAT serine kinase in CLL cells has not been identified, and appears to be neither mitogen-activated protein kinase nor pp70(s6k). In summary, the constitutive serine phosphorylation of STAT1 and **STAT3** is present in all CLL samples tested to date, although the physiologic significance of this modification remains to be determined.

L3 ANSWER 9 OF 34 MEDLINE
ACCESSION NUMBER: 1998054332 MEDLINE
DOCUMENT NUMBER: 98054332 PubMed ID: 9391124
TITLE: Proliferation of adult T cell leukemia/lymphoma cells is associated with the constitutive activation of JAK/STAT proteins.
AUTHOR: Takemoto S; Mulloy J C; Cereseto A; Migone T S; Patel B K; Matsuoka M; Yamaguchi K; Takatsuki K; Kamihira S; White J D; Leonard W J; Waldmann T; Franchini G
CORPORATE SOURCE: Basic Research Laboratory, Division of Basic Sciences, National Cancer Institute, Bethesda, MD 20892, USA.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1997 Dec 9)** 94 (25) 13897-902.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980115

AB Human T cell leukemia/lymphotropic virus type I (HTLV-I) induces adult T cell leukemia/lymphoma (ATLL). The mechanism of HTLV-I oncogenesis in T cells remains partly elusive. In vitro, HTLV-I induces ligand-independent transformation of human CD4+ T cells, an event that correlates with acquisition of constitutive phosphorylation of Janus kinases (JAK) and signal transducers and activators of transcription (STAT) proteins.

However, it is unclear whether the in vitro model of HTLV-I transformation has relevance to viral leukemogenesis in vivo. Here we tested the status of JAK/STAT phosphorylation and DNA-binding activity of STAT proteins in cell extracts of uncultured leukemic cells from 12 **patients** with ATLL by either DNA-binding assays, using DNA oligonucleotides specific for STAT-1 and STAT-3, STAT-5 and STAT-6 or, more directly, by immunoprecipitation and immunoblotting with anti-phosphotyrosine antibody for JAK and STAT proteins. Leukemic cells from 8 of 12 **patients** studied displayed constitutive DNA-binding activity of one or more STAT proteins, and the constitutive activation of the JAK/STAT pathway was found to persist over time in the 2 **patients** followed longitudinally. Furthermore, an association between JAK3 and STAT-1, STAT-3, and STAT-5 activation and cell-cycle progression was demonstrated by both propidium iodide staining and bromodeoxyuridine incorporation in cells of four **patients** tested. These results imply that JAK/STAT activation is associated with replication of leukemic cells and that therapeutic approaches aimed at JAK/STAT inhibition may be considered to halt neoplastic growth.

L3 ANSWER 10 OF 34 MEDLINE
ACCESSION NUMBER: 97422541 MEDLINE
DOCUMENT NUMBER: 97422541 PubMed ID: 9278309
TITLE: IL-6 triggers cell growth via the Ras-dependent mitogen-activated protein kinase cascade.
AUTHOR: Ogata A; Chauhan D; Teoh G; Treon S P; Urashima M; Schlossman R L; Anderson K C
CORPORATE SOURCE: Dana-Farber Cancer Institute, and Department of Medicine, Harvard Medical School, Boston, MA 02215, USA.
CONTRACT NUMBER: CA 50947 (NCI)
SOURCE: JOURNAL OF IMMUNOLOGY, **(1997 Sep 1)** 159 (5) 2212-21.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19971008
Last Updated on STN: 20000303
Entered Medline: 19970919

AB IL-6 mediates growth of some human multiple myeloma (MM) cells and IL-6-dependent cell lines. Although three IL-6 signaling pathways (STAT1, **STAT3**, and Ras-dependent MAPK cascade) have been reported, cascades mediating IL-6-triggered growth of MM cells and cell lines are not defined. In this study, we therefore characterized IL-6 signaling cascades in MM cell lines, MM **patient** cells, and IL-6-dependent B9 cells to determine which pathway mediates IL-6-dependent growth. IL-6 induced phosphorylation of JAK kinases and gp130, regardless of the proliferative response of MM cells to this growth factor. Accordingly, we next examined downstream IL-6 signaling via the **STAT3**, STAT1, and Ras-dependent mitogen-activated protein kinase (MAPK) cascades. IL-6 triggered phosphorylation of STAT1 and/or **STAT3** in MM cells independent of their proliferative response to IL-6. In contrast, IL-6 induced phosphorylation of Shc and its association with Sos1, as well as phosphorylation of MAPK, only in MM cells and B9 cells that proliferated in response to IL-6. Moreover, MAPK antisense, but not sense, oligonucleotide inhibited IL-6-induced proliferation of these cells. These

data suggest that STAT1 and/or **STAT3** activation may occur independently of the proliferative response to IL-6, and that activation of the MAPK cascade is an important distal pathway for IL-6-mediated growth.

L3 ANSWER 11 OF 34 MEDLINE
ACCESSION NUMBER: 97338092 MEDLINE
DOCUMENT NUMBER: 97338092 PubMed ID: 9192639
TITLE: Constitutive activation of a slowly migrating isoform of **Stat3** in mycosis fungoides: tyrphostin AG490 inhibits **Stat3** activation and growth of mycosis fungoides tumor cell lines.
AUTHOR: Nielsen M; Kaltoft K; Nordahl M; Ropke C; Geisler C; Mustelin T; Dobson P; Svejgaard A; Odum N
CORPORATE SOURCE: Institute of Medical Microbiology and Immunology, Section A, University of Copenhagen, 2200 N Copenhagen, Denmark.. M.Nielsen@SB.IMMI.KU.DK
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1997 Jun 24)** 94 (13) 6764-9.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970805
Last Updated on STN: 19970805
Entered Medline: 19970721

AB Mycosis fungoides (MF) is a low-grade cutaneous T cell lymphoma of unknown etiology. In this report, the Jak/Stat (Janus kinase/signal transducer and activator of transcription) signaling pathway was investigated in tumor cell lines established from skin biopsy specimens from a **patient** with MF. Jaks link cytokine receptors to Stats, and abnormal Jak/Stat signaling has been observed in some hemopoietic cancers. In MF tumor cells, a slowly migrating isoform of **Stat3**, **Stat3**(sm), was found to be constitutively activated, i.e., (i) **Stat3**(sm) was constitutively phosphorylated on tyrosine residues, and tyrosine phosphorylation was not enhanced by growth factor stimulation; (ii) band shift assays and immunoprecipitations of DNA/Stat complexes showed constitutive DNA-binding properties of **Stat3**(sm); and (iii) **Stat3**(sm) was constitutively associated with Jak3. The abnormal activation of **Stat3**(sm) was highly specific. Thus, neither the fast migrating isoform of **Stat3** (**Stat3**(fm)) nor other Stats (Stat1, Stat2, and Stat4 through Stat6) were constitutively activated. The Jak kinase inhibitor, tyrphostin AG490, blocked the constitutive activation of **Stat3**(sm) and inhibited spontaneous as well as interleukin 2-induced growth of MF tumor cells. In conclusion, we have provided evidence for an abnormal Jak/Stat signaling and growth regulation in tumor cells obtained from affected skin of an MF **patient**.

L3 ANSWER 12 OF 34 MEDLINE
ACCESSION NUMBER: 97309442 MEDLINE
DOCUMENT NUMBER: 97309442 PubMed ID: 9166857
TITLE: Characterization of interleukin-10 receptor expression on B-cell chronic lymphocytic leukemia cells.
AUTHOR: Jurlander J; Lai C F; Tan J; Chou C C; Geisler C H;

Schriber J; Blumenson L E; Narula S K; Baumann H; Caligiuri M A

CORPORATE SOURCE: Department of Molecular and Cell Biology, Roswell Park Cancer Institute, Buffalo, NY 14263, USA.

CONTRACT NUMBER: CA26122 (NCI)
CA65670 (NCI)
DK33886 (NIDDK)
+
SOURCE: BLOOD, **(1997 Jun 1)** 89 (11) 4146-52.
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 19970630
Entered Medline: 19970617

AB B-cell chronic lymphocytic leukemia (B-CLL) cells accumulate in vivo in the G0/G1 phase of the cell cycle, suggesting that their malignant expansion is due, at least in part, to a delay in cell death. However, the cellular or molecular factors responsible for a delay in B-CLL cell death are unknown. B-CLL cells do express receptors for interferon-alpha (IFN-alpha) and IFN-gamma, and activation of both has been shown to promote B-CLL survival in vitro by preventing apoptosis. The interleukin-10 (IL-10) receptor is another member of the IFN receptor family, but its ligand, IL-10, has been reported to induce apoptosis in B-CLL cells. In the current study, we undertook a biochemical analysis of IL-10 receptor expression on freshly isolated B-CLL cells and characterized the functional responsiveness of IL-10 binding to its constitutively expressed receptor. We show that B-CLL cells bind IL-10 with significant specificity and express between 47 and 127 IL-10 receptor sites per cell, with a dissociation constant in the range of 168 to 426 x 10(-12) mol/L. Ligand binding and activation of the IL-10 receptor expressed on B-CLL cells results in the phosphorylation of signal transducer and activator of transcription 1 (STAT1) and **STAT3** proteins. This pattern of STAT protein phosphorylation is identical to IL-10 receptor activation on normal cells and similar to IFN-alpha (STAT1 and **STAT3**) and IFN-gamma (STAT1) receptor activation in CLL. Further, in consecutive samples of fresh blood obtained from **patients** with B-CLL cells, the addition of IL-10 inhibited B-CLL proliferation, enhanced B-CLL differentiation, but did not induce apoptosis. Indeed, IL-10, like IFN-gamma, was able to significantly reduce the amount of B-CLL cell death caused by hydrocortisone-induced apoptosis.

We conclude that cytokines, which signal through the interferon family of receptors, have comparable functional effects on B-CLL cells.

L3 ANSWER 13 OF 34 MEDLINE

ACCESSION NUMBER: 97174344 MEDLINE
DOCUMENT NUMBER: 97174344 PubMed ID: 9022078
TITLE: Differential human multiple myeloma cell line responsiveness to interferon-alpha. Analysis of transcription factor activation and interleukin 6 receptor expression.
AUTHOR: Jelinek D F; Aagaard-Tillery K M; Arendt B K; Arora T;

Tschumper R C; Westendorf J J
CORPORATE SOURCE: Department of Immunology, Mayo Clinic/Foundation, Rochester, Minnesota 55905, USA.. jelinek.diane@mayo.edu
CONTRACT NUMBER: CA62228 (NCI)
CA62242 (NCI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, **(1997 Feb 1)** 99 (3) 447-56.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970321
Last Updated on STN: 19970321
Entered Medline: 19970310

AB Although IFN-alpha is commonly used as maintenance treatment for multiple myeloma **patients**, its effectiveness is varied. In this study, we have used a panel of IL-6 responsive myeloma cell lines that vary remarkably in responsiveness to IFN-alpha. Three cell lines were growth arrested by IFN-alpha; however, IFN-alpha significantly stimulated growth of the fourth cell line, KAS-6/1. Our studies have focused on elucidating the mechanism of differential IFN-alpha responsiveness. First, we have shown that IFN-alpha-stimulated growth of the KAS-6/1 cells did not result from induction of autocrine IL-6 expression. Second, analysis of Stats 1, 2, and 3 and IFN regulatory factor-1 (IRF-1) and IRF-2 activation failed to reveal differences between the IFN-alpha growth-arrested or growth-stimulated cells. Third, although IFN-alpha treatment of the IFN-alpha growth-inhibited cell lines reduced IL-6 receptor (IL-6R) expression, IFN-alpha also reduced KAS-6/1 IL-6R expression. Finally, although IFN-alpha treatment reduced IL-6R numbers on each cell line, analysis of Stat protein activation revealed that the receptors were still functional. We conclude that myeloma cell responsiveness to IFN-alpha is heterogeneous and that mechanisms of IFN-alpha-mediated growth inhibition other than IL-6R downregulation must exist in myeloma. Identification of these mechanisms may allow development of agents that are more universally effective than IFN-alpha.

L3 ANSWER 14 OF 34 MEDLINE
ACCESSION NUMBER: 96437018 MEDLINE
DOCUMENT NUMBER: 96437018 PubMed ID: 8839834
TITLE: Granulocyte colony-stimulating factor activation of **Stat3** alpha and **Stat3** beta in immature normal and leukemic human myeloid cells.
AUTHOR: Chakraborty A; White S M; Schaefer T S; Ball E D; Dyer K F;
Tweardy D J
CORPORATE SOURCE: Department of Medicine, University of Pittsburgh School of Medicine, PA, USA.
CONTRACT NUMBER: AI07333 (NIAID)
CA31888 (NCI)
SOURCE: BLOOD, **(1996 Oct 1)** 88 (7) 2442-9.
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961107

AB Granulocyte colony-stimulating factor (G-CSF) is the cytokine critical for directing neutrophilic granulocyte differentiation. Acute myelogenous leukemia (AML) cells, which frequently arise from this lineage, respond aberrantly to G-CSF by proliferating without differentiating. The basis for this abnormal responses is unknown. In the present study, we investigated whether G-CSF signaling in immature normal and leukemic human myeloid cells diverges at the level of activation of signal transducers and activators of transcription (STAT) proteins. We compared the profile of STAT proteins activated in G-CSF-stimulated immature normal and leukemic human myeloid cells. G-CSF activated **Stat3** alpha in all AML cell lines examined except HL60 and in three of six uncultured AML **patient** samples. In normal human CD34+ bone marrow cells and HL60 cells, both reported to differentiate in response to G-CSF, G-CSF did not activate **Stat3** alpha; rather, it activated only an 83 kD form of **Stat3** that proved to be the human homologue of a short form of **Stat3**, **Stat3** beta. Because the transcriptional activity of **Stat3** beta is distinct from **Stat3** alpha, these results suggest that the balance of the two **Stat3** isoforms in myeloid cells may influence the cellular pattern of gene activation and consequently the ability of these cells to differentiate in response to G-CSF.

L3 ANSWER 15 OF 34 MEDLINE
ACCESSION NUMBER: 96392381 MEDLINE
DOCUMENT NUMBER: 96392381 PubMed ID: 8799169
TITLE: Activation of Jak/STAT proteins involved in signal transduction pathway mediated by receptor for interleukin 2 in malignant T lymphocytes derived from cutaneous anaplastic large T-cell lymphoma and Sezary syndrome.
AUTHOR: Zhang Q; Nowak I; Vonderheid E C; Rook A H; Kadin M E; Nowell P C; Shaw L M; Wasik M A
CORPORATE SOURCE: Department of Pathology, University of Pennsylvania Medical Center, Philadelphia 19104, USA.
CONTRACT NUMBER: CA-42232 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1996 Aug 20)** 93 (17) 9148-53.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19990129
Entered Medline: 19961031

AB Signaling through the interleukin 2 receptor (IL-2R) involves phosphorylation of several proteins including Jak3, STAT5, and, in preactivated cells, **STAT3**. In the present study, we examined the functional status of the IL-2R-associated Jak/STAT pathway in malignant T lymphocytes from advanced skin-based lymphomas: anaplastic large T-cell lymphoma (ALCL) and Sezary syndrome (SzS). Proliferation of three ALCL

cell lines (PB-1, 2A, and 2B) was partially inhibited by rapamycin, a blocker of some of the signals mediated by IL-2R, but not by cyclosporin A, FK-506, and prednisone, which suppress signals mediated by the T-cell receptor. All the cell lines expressed on their surface the high-affinity IL-2R (alpha, beta, and gamma c chains). They showed basal, constitutive phosphorylation, and coassociation of Jak3, STAT5, and **STAT3**. Weak basal phosphorylation of IL-2R gamma c was also detected. In regard to SzS, peripheral blood mononuclear cells from 10 of 14 **patients** showed basal phosphorylation of Jak3, accompanied by phosphorylation of STAT5 in 9 **patients**, and **STAT3** in 4 **patients** . However, in vitro overnight culture of SzS cells without exogenous cytokines resulted in markedly decreased Jak3 and STAT5 phosphorylation, which could be reversed by stimulation with IL-2. This indicates that the basal phosphorylation of Jak3 and STAT5 in freshly isolated SzS cells is induced rather than constitutive. The basal activation of the Jak/STAT pathway involved in IL-2R signal transduction in ALCL and SzS cells reported here suggests that this pathway may play a role in the pathogenesis of cutaneous T-cell lymphomas, although the mechanism (induced versus constitutive) may vary between different lymphoma types.

L3 ANSWER 16 OF 34 MEDLINE
ACCESSION NUMBER: 96309621 MEDLINE
DOCUMENT NUMBER: 96309621 PubMed ID: 8704235
TITLE: Constitutive activation of STAT proteins in primary lymphoid and myeloid leukemia cells and in Epstein-Barr virus (EBV)-related lymphoma cell lines.
AUTHOR: Weber-Nordt R M; Egen C; Wehinger J; Ludwig W; Gouilleux-Gruart V; Mertelsmann R; Finke J
CORPORATE SOURCE: Department of Hematology & Oncology, Albert-Ludwigs-University Medical Center, Freiburg, Germany.
SOURCE: BLOOD, **(1996 Aug 1)** 88 (3) 809-16.
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960919
Last Updated on STN: 19980206
Entered Medline: 19960912

AB Although various molecular mechanisms of STAT protein (signal transducers and activators of transcription) activation have been identified, little is known about the functional role of STAT-dependent transcriptional activation. Herein we report the constitutive nuclear localization, phosphorylation, and DNA-binding activity of STAT proteins in leukemia cells and lymphoma cell lines. With the use of oligonucleotide probes derived from the Fc gamma RI promoter, the beta-casein promoter and a STAT-binding element in the promoter of the Bci-2 gene constitutive activation of STAT proteins was detected in untreated acute T- and C/B-leukemia cells (3 of 5 and 12 of 19 **patients**, respectively). Supershift analyses using Stats 1-6 specific antisera showed the constitutive DNA binding activity of Stat5 in these cells. Confocal microscopy revealed the nuclear localization of Stat5 and Western blot analyses showed tyrosine phosphorylation of Stat5 in nuclear extracts of acute leukemia cells. In contrast, peripheral blood mononuclear cells did not display constitutive STAT-DNA interaction. Further studies were performed on freshly isolated acute myeloid leukemia cells as well as on cell line derived K562, lymphoblastoid cells (LCL), and Burkitt's lymphoma cells (BL). Fluorescence microscopy, gelshift, and supershift experiments

showed the nuclear localization and constitutive DNA-binding activity of Stat5 in K562 cells. Stat1 and **Stat3** were constitutively activated in freshly isolated AML cells (10 of 14 **patients**) and in Epstein Barr virus-positive or interleukin-10 expressing permanent LCL and BL cells. Thus, these data indicate a differential pattern of STAT protein activation in lymphoid or myeloid leukemia and in lymphoma cells.

L3 ANSWER 17 OF 34 MEDLINE
ACCESSION NUMBER: 96290415 MEDLINE
DOCUMENT NUMBER: 96290415 PubMed ID: 8704165
TITLE: Retinoic acid activates interferon regulatory factor-1 gene expression in myeloid cells.
AUTHOR: Matikainen S; Ronni T; Hurme M; Pine R; Julkunen I
CORPORATE SOURCE: Molecular Biology Programme, National Public Health Institute, Helsinki, Finland.
SOURCE: BLOOD, **(1996 Jul 1)** 88 (1) 114-23.
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960919
Last Updated on STN: 19970203
Entered Medline: 19960909

AB All-trans-retinoic acid (ATRA) is the drug of choice in the treatment of acute promyelocytic leukemia (APL). ATRA induces both in vitro and in vivo differentiation of APL cells into mature granulocytes. However, the molecular mechanisms involved in ATRA-dependent growth inhibition and cellular differentiation are not presently understood. The NB4 cell line, which is derived from the bone marrow of a **patient** with APL during relapse, can be used as a model system to study the growth and differentiation of APL cells. Because interferon (IFN) regulatory factors (IRF-1 and IRF-2) and other IFN-inducible gene products regulate cell growth, we analyzed the effects of ATRA on the expression of these genes. We show that ATRA directly activates IRF-1 gene expression, followed by activation of IRF-2 and 2'-5' oligoadenylate synthetase (OAS) gene expression with slower kinetics. In addition to NB4 cells, ATRA also activated IRF-1 gene expression in HL-60, U937, and THP-1 cells, which all respond to ATRA by growth inhibition. A more than additive increase in IRF-1 gene expression was seen with ATRA and IFN-gamma in NB4 cells. ATRA did not activate nuclear factor kappa B or signal transducer and activator of transcription (STAT) activation pathways, suggesting that an alternate mechanism is involved in IRF-1 gene activation. The ATRA-induced expression of IRF-1, an activator of transcription and repressor of transformation, may be one of the molecular mechanisms of ATRA-induced growth inhibition, and the basis for the synergistic actions of ATRA and IFNs in myeloid leukemia cells.

L3 ANSWER 18 OF 34 MEDLINE
ACCESSION NUMBER: 96202489 MEDLINE
DOCUMENT NUMBER: 96202489 PubMed ID: 8634413
TITLE: STAT-related transcription factors are constitutively activated in peripheral blood cells from acute leukemia **patients**.
AUTHOR: Gouilleux-Gruart V; Gouilleux F; Desaint C; Claisse J F;

Capiod J C; Delobel J; Weber-Nordt R; Dusanter-Fourt I; Dreyfus F; Groner B; Prin L
CORPORATE SOURCE: Laboratoire d'Immunologie, Centre Hospitalier Universitaire d'Amiens, France.
SOURCE: BLOOD, **(1996 Mar 1)** 87 (5) 1692-7.
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960719
Last Updated on STN: 19970203
Entered Medline: 19960710

AB A signal transduction pathway activated by many cytokines has recently been elaborated. The JAK kinases and the signal transducers and activators of transcription (STAT) factors have been found to be essential components. In this report, we describe the presence of constitutively activated STAT factors in peripheral blood cells from **patients** with acute leukemia. We used oligonucleotide probes from the beta-casein and IRF-1 gene promoters and the ISRE probe to detect STAT proteins in nuclear extracts from acute leukemia cells in bandshift assays. Specific DNA protein complex formation was observed with the probes from the beta-casein and IRF-1 gene promoters, but not with the ISRE oligonucleotide probe, when cell extracts from acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) were investigated. We used nonradioactive oligonucleotides as competitors to show the specificity of the complex formation. Specific antibodies directed against the individual STAT proteins were used in supershift experiments. STAT5- and STAT1-related factors were detected in ALL and STAT1-, **STAT3-**, and STAT5-related proteins were present in nuclear cell extracts from AML. Since the cells were not treated with cytokines before the nuclear proteins were extracted, we conclude that these factors are constitutively activated in vivo. It is likely that the constitutive activation of STAT proteins is a part of the events of leukemogenesis.

L3 ANSWER 19 OF 34 MEDLINE
ACCESSION NUMBER: 96096457 MEDLINE
DOCUMENT NUMBER: 96096457 PubMed ID: 7500028
TITLE: Regulation of the balance of cytokine production and the signal transducer and activator of transcription (STAT) transcription factor activity by cytokines and inflammatory synovial fluids.
AUTHOR: Wang F; Sengupta T K; Zhong Z; Ivashkiv L B
CORPORATE SOURCE: Department of Medicine, Hospital for Special Surgery, New York, USA.
CONTRACT NUMBER: K08 AR-01852 (NIAMS)
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, **(1995 Dec 1)** 182 (6) 1825-31.
Journal code: I2V; 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199601
ENTRY DATE: Entered STN: 19960217
Last Updated on STN: 19960217
Entered Medline: 19960117

AB The balance between type 1 and 2 T helper cell cytokine production plays an important role in several animal models of autoimmunity, and skewed patterns of cytokine expression have been described in human inflammatory diseases. Many cytokines activate signal transducer and activation of transcription (STAT) transcription factors, which, in turn, activate transcription of inflammatory effector genes. We used mononuclear cell priming cultures and inflammatory synovial fluids (SFs) derived from arthritis **patients** to examine the regulation of cytokine production and STAT activity by an inflammatory synovial microenvironment.

Exposure to SFs during priming resulted in an 81% inhibition of interferon (IFN)-gamma, but not interleukin (IL) 4, production by effector cells generated in priming cultures. SF suppression was mediated by IL-4 and IL-10 and inhibition of IL-12 expression, and it was reversed in a dominant fashion by exogenous IL-12. SFs blocked the sustained activity of transcription factor Stat1, but not **Stat3**, during the priming period, and Stat1 activity was differentially regulated by cytokines in parallel with their positive or negative regulation of IFN-gamma production. Active **Stat3**, but not Stat1, was detected in cells from inflamed joints. These results suggest a role for altered balance of Stat1 and **Stat3** transcriptional activity in the regulation of T cell differentiation and in the pathogenesis of inflammatory synovitis.

L3 ANSWER 20 OF 34 CANCERLIT
ACCESSION NUMBER: 1998639977 CANCERLIT
DOCUMENT NUMBER: 98639977
TITLE: Sodium butyrate induces tyrosine phosphorylation of STAT2 and **STAT3** in K562 erythroleukemia cells (Meeting abstract).
AUTHOR: Anonymous
CORPORATE SOURCE: Meharry Medical College, Dept. of Biochemistry and Comprehensive Sickle Cell Center, Nashville, TN 37208.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, **(1997)**. Vol. 38, pp. A2977.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199808

AB Pharmacological manipulation of cell growth and differentiation can benefit individuals suffering from cancer. The clinical benefits resulting from such treatment is due to an increase in the production of fetal hemoglobin during erythroid maturation. However, the fact that drugs such as hydroxyurea may be toxic and have potential carcinogenic effects raises the need for compounds that will serve as safe alternatives. Sodium butyrate (NaB) is specific in inducing fetal globin gene synthesis in sickle cell **patients** as well as induce differentiation and apoptosis in a number of cancer cell lines. However, the mechanism by which this agent regulates growth remains unknown. The purpose of this study was to determine the effect of 1 mM NaB on (1) tyrosine phosphorylation of members of the STAT family, as well as (2) the

translocation of the STAT proteins to the nucleus. Evidence from immunoprecipitation and immuno-blotting studies demonstrates that NaB induces tyrosine phosphorylation of STAT2 and **STAT3**. Nuclear translocation of STAT-3 was seen 5 minutes after NaB treatment. The findings that STAT proteins are tyrosine phosphorylated upon NaB treatment provide the first evidence that the JAK/STAT signaling pathway may be involved in the NaB signaling mechanism. Research is ongoing to determine the effects of NaB on tyrosine phosphorylation and activation of members of the JAK family.

L3 ANSWER 21 OF 34 CANCERLIT
ACCESSION NUMBER: 1998637782 CANCERLIT
DOCUMENT NUMBER: 98637782
TITLE: Interferon-alpha resistance in a cutaneous T cell lymphoma cell line is associated with loss of the STAT1 protein (Meeting abstract).
AUTHOR: Sun W H; Jandeska S; Pabon C; Rosen S T
CORPORATE SOURCE: Lurie Cancer Center, Northwestern University Medical School, Chicago, IL 60614.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, **(1997)**. Vol. 38, pp. A782.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199801

AB Cutaneous T cell lymphoma (CTCL) is characterized by a clonal malignant proliferation of mature helper T cells in the skin with ultimate progression involving lymph nodes, peripheral blood and viscera. Administration of recombinant interferon alpha-2a (IFNalpha-2a) has been shown to be one of the most effective therapies for CTCL. However, the efficacy of IFNalpha-2a is limited by the development of resistance in some **patients** who received continuous therapy. IFNalpha belongs to the Type-I IFN family and binds to the Type-I IFN receptor (IFNR). Phosphorylation of IFNR, immediately after ligand binding, is regulated by two Janus kinases (Tyk-2 and Jak-1). Tyk-2 and Jak-1 themselves also become phosphorylated in cells upon IFNalpha stimulation. The activated Tyk-2 and Jak-1 then induce phosphorylation of interferon-regulated signal transducers and activators of transcription (STATs). Activated STAT 1 and 2 can associate with a 48 kD protein (p48) to form the interferon-stimulated gene factor-3 (ISGF-3) complex which binds specifically to the IFNalpha-stimulated response element (ISRE), resulting in gene transcription. More recently, **STAT3** was reported to be phosphorylated upon IFNalpha treatment and form a protein-DNA complex, distinct from the ISGF3 complex. We have developed an IFN resistant CTCL cell line (HUT78R) by culturing the IFN-sensitive cells (HUT78S) in increasing concentration of IFNalpha-2a (up to 1 x 10(6) U/ml) for a prolonged period. The levels of IFNR mRNA expression were found to be comparable between the two lines, by Northern and Slot blot analyses. The HUT78R and S lines also exhibited similar levels of binding sites and binding affinity for 125I-labeled recombinant IFNalpha-2a determined by Scatchard analysis. By gel shift analysis, we found that IFNalpha induced the ISGF3 complex formation using the labeled ISRE probe and this DNA-protein interaction was inhibited in the HUT78R cells. We then examined STAT protein activation in HUT78 cells and our results showed that phosphorylation of STAT1 was completely inhibited in the resistant

cells. However, IFNalpha-induced STAT2 phosphorylation was comparable between the HUT78R and HUT78S lines. Both lines exhibited a low level of constitutive **STAT3** phosphorylation and an increased level of **STAT3** phosphorylation can be induced upon IFNalpha-2a treatment. To our surprise, we did not detect any STAT1 (alpha and beta) protein in the HUT78R cells by immunoblotting analysis. RT-PCR results revealed that both cell lines contain the STAT1 transcript, using primers encoding the first five exons. However, it is not clear if there are mutation(s) further downstream that may cause premature termination of the transcript. We are currently investigating these possibilities. In summary, our findings suggest that IFNalpha-resistance are caused by the loss of STAT1 protein in a human cancer cell line.

L3 ANSWER 22 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:89298 BIOSIS
DOCUMENT NUMBER: PREV199900089298
TITLE: IL-6 receptor (CD126'IL-6R') expression is increased on monocytes and B lymphocytes in HIV infection.
AUTHOR(S): van Der Meijden, Meta (1); Gage, Julia; Breen, Elizabeth Crabb; Taga, Tetsuya; Kishimoto, Tadamitsu; Martinez-Maza, Ontoniel
CORPORATE SOURCE: (1) Dep. Microbiol., UCLA Sch. Med., Los Angeles, CA USA
SOURCE: Cellular Immunology, (**Dec. 15, 1998**) Vol. 190, No. 2, pp. 156-166.
ISSN: 0008-8749.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Interleukin-6 (IL-6) is a multifunctional cytokine, with a wide range of effects on various cell types, including several types of cells involved in immune responses. IL-6 is believed to be involved in the pathogenesis of several diseases and may contribute to AIDS pathogenesis in various ways. Elevated levels of IL-6 occur in HIV infection. The objective of this study was to define the distribution of the expression of the 80-kDa alpha subunit of the IL-6 receptor (CD126'IL-6R') on immune cell subpopulations in HIV-infected subjects. CD126 is responsible for IL-6 binding, and its expression determines which cells respond to this cytokine. An elevated number of monocytes, B cells, and CD4 T cells expressing CD126 were seen in the peripheral circulation of HIV-infected subjects when compared to HIV-seronegative control subjects. Also, an increase in the density of CD126 expression was noted on monocytes. Generally, the observed increases in CD126 did not correlate with CD4 levels in HIV-infected subjects or with disease status, with the exception of CD126 expression on CD8 T cells, which was lower in those HIV-infected subjects that had AIDS. In some cases, increased CD126 expressing cells showed higher levels of **STAT3** phosphorylation on exposure to recombinant IL-6. These results indicate that greatly elevated levels of CD126-expressing cells, particularly B cells and monocytes, are seen in HIV infection and suggest that the altered expression of CD126 may contribute directly or indirectly to immune dysfunction and to AIDS pathogenesis in HIV infection.

L3 ANSWER 23 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:479394 BIOSIS
DOCUMENT NUMBER: PREV199800479394
TITLE: Analysis of liver regeneration in mice lacking type 1 or type 2 tumor necrosis factor receptor: Requirement for type 1 but not type 2 receptor.

AUTHOR(S): Yamada, Yasuhiro; Webber, Eric M.; Kirillova, Irina; Peschon, Jacques J.; Fausto, Nelson (1)
CORPORATE SOURCE: (1) Dep. Pathology, Box 357705, Univ. Washington Sch. Med., K-078 Fialkow Biomedical Res. Pavilion, Seattle, WA 98195-7705 USA
SOURCE: Hepatology, (**Oct., 1998**) Vol. 28, No. 4, pp. 959-970.
ISSN: 0270-9139.
DOCUMENT TYPE: Article
LANGUAGE: English
AB We used KO mice lacking either TNF receptor 1 (TNFR-1) or receptor 2 (TNFR-2) to determine whether signaling at the start of liver regeneration after partial hepatectomy (PH) involves only one or both TNF receptors and to analyze in more detail the abnormalities caused by lack of TNFR-1 receptor, which is required for the initiation of liver regeneration. Lack of TNFR-2 had little effect on NF-kappaB and **STAT3** binding, and no effect in interleukin-6 production after PH, but caused a delay in AP-1 and C/EBP binding and in the expression of c-jun and c-myc messenger RNA (mRNA). In contrast to mice lacking TNFR-1, which had deficient hepatocyte DNA synthesis and massive lipid accumulation in hepatocytes, TNFR-2 KO mice had normal liver structure and similar levels of hepatocyte DNA replication as those of wild type mice. We conclude that TNFR-1, but not TNFR-2, is necessary for liver regeneration, and that NF-kappaB and **STAT3** binding are activated by signals transduced by TNFR-1. Inhibition of AP-1 and C/EBP binding and in the expression of c-jun and c-myc mRNA in the first 4 hours after PH, as well as the apparent lack of Fos in AP-1 complexes, had no effect on the timing or extent of DNA replication.

L3 ANSWER 24 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:419089 BIOSIS
DOCUMENT NUMBER: PREV199800419089
TITLE: Multiple mechanisms of **STAT3** activation by the human granulocyte colony-stimulating factor receptor.
AUTHOR(S): Ward, A. C. (1); Smith, L.; Van Aesch, Y. M.; Schelen, A.; Touw, I. P. (1)
CORPORATE SOURCE: (1) Inst. Hematol., Erasmus Univ. Rotterdam, Rotterdam Netherlands
SOURCE: British Journal of Haematology, (**July 1, 1998**) Vol. 102, No. 1, pp. 154-155.
Meeting Info.: Combined Haematology Congress of the International Society of Haematology and the European Hematology Association Amsterdam, Netherland July 4-8, 1998
ISSN: 0007-1048.
DOCUMENT TYPE: Conference
LANGUAGE: English

L3 ANSWER 25 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:406305 BIOSIS
DOCUMENT NUMBER: PREV199800406305
TITLE: Variations in the levels of the JAK/STAT and ShcA proteins in human brain tumors.
AUTHOR(S): Cattaneo, Elena (1); Magrassi, Lorenzo; De-Fraja, Claudio;

Conti, Luciano; Di Gennaro, Immacolata; Butti, Giorgio; Govoni, Stefano

CORPORATE SOURCE: (1) Inst. Pharmacol. Sci., Univ. Milano, Via Balzaretti 9, 20133 Milano Italy

SOURCE: Anticancer Research, (**July-Aug., 1998**) Vol. 18, No. 4A, pp. 2381-2387.
ISSN: 0250-7005.

DOCUMENT TYPE: Article
LANGUAGE: English

AB Background: Recent demonstrations that the JAK/STAT and ShcA signalling proteins are abundant in the developing CNS at the stage of maximal cell proliferation prompted us to determine whether these proteins were expressed in various human brain tumors. Materials and Methods: Using Western blot assay, we analyzed specimens from control peritumoral brain tissue, medulloblastomas, ependymomas, astrocytomas, anaplastic astrocytomas and glioblastomas. Results: Our analyses revealed that Jak1 and **Stat3** were consistently more elevated in low grade gliomas (LG) (tumors characterized by a more pronounced glial phenotype) as compared to high grade gliomas (HG) (less differentiated glial tumors). The other STAT proteins were equally expressed, while Stat1 was slightly higher in LG gliomas. Among the other tumors analyzed, medulloblastoma contained the highest level of Jak1 and **Stat3**, while ependymoma showed elevated levels of ShcA proteins. Conclusions: These differences may reflect differences in the biological characteristics of the various tumors and may provide insight for further mechanistic studies to investigate the importance of particular signal transduction pathways in CNS tumors.

L3 ANSWER 26 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1998:357288 BIOSIS
DOCUMENT NUMBER: PREV199800357288

TITLE: Erythropoietin induces tyrosine phosphorylation of Jak2, STAT5A, and STAT5B in primary cultured human erythroid precursors.

AUTHOR(S): Oda, Atsushi (1); Sawada, Kenichi; Druker, Brian J.; Ozaki, Katsutoshi; Takano, Hina; Koizumi, Kazuki; Fukada, Yoshikazu; Handa, Makoto; Koike, Takao; Ikeda, Yasuo

CORPORATE SOURCE: (1) Dep. Internal Med., Sch. Med., Keio Univ., 35 Shinanoma-chi, Tokyo 160 Japan

SOURCE: Blood, (**July 15, 1998**) Vol. 92, No. 2, pp. 443-451.
ISSN: 0006-4971.

DOCUMENT TYPE: Article
LANGUAGE: English

AB We examined signaling by erythropoietin in highly purified human colony forming unit-erythroid cells, generated in vitro from CD34+ cells. We found that erythropoietin induces tyrosine phosphorylation of Jak2, STAT5A, and STAT5B. Tyrosine phosphorylation of Jak2 reaches a peak around 10 minutes after stimulation and is maximum at 5 U/mL of erythropoietin. Tyrosine phosphorylation of STAT5 is accompanied by the translocation of activated STAT5 to the nucleus as shown by electrophoretic mobility shift assay (EMSA) using 32Pi-labeled STAT5 binding site in the beta-casein promoter. Tyrosine phosphorylation STAT1 or **STAT3** was not detected in human erythroid precursors after stimulation with erythropoietin. Crkl, an SH2/SH3 adapter protein, becomes coimmunoprecipitated specifically with STAT5 from erythropoietin-stimulated erythroid cells; although it was shown to become associated with c-Cbl in the studies using cell lines. Thus, human erythroid

precursors can be expanded in vitro in sufficient numbers and purity to allow its usage in signal transduction studies. This report sets a basis for further studies on signaling in primary cultured human erythroid precursors, which in turn contribute to our better understanding in the differentiation processes of erythrocytes and their precursors.

L3 ANSWER 27 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:160051 BIOSIS
DOCUMENT NUMBER: PREV199800160051
TITLE: G-CSF induced STAT1 and **STAT3** kinetics of activation are normal in G-CSF sensitive t(8;21) AML cells.
AUTHOR(S): Da Silva, Nicolas; Meyer-Monard, Sandrine; Bastie, Jean-Noel; Dombret, Herve; Degos, Laurent; Chomienne, Christine
CORPORATE SOURCE: Lab. Biologie Cellularie Hematopoietique, Inst. Hematologie, Hopital Saint-Louis, 1 ave. Claude Vellefaux, 75475 Paris Cedex 10 France
SOURCE: Leukemia (Basingstoke), (**Dec., 1997**) Vol. 11, No. 12, pp. 2225.
Meeting Info.: First Meeting on Acute Leukemias with Structurally Altered Core Binding Factor Subunits (t(8;21), inv(16) and t(12;21)) Rotterdam, Netherlands June 27-28, 1997
ISSN: 0887-6924.
DOCUMENT TYPE: Conference
LANGUAGE: English

L3 ANSWER 28 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:109555 BIOSIS
DOCUMENT NUMBER: PREV199800109555
TITLE: G-CSF induced STAT1 and **STAT3** kinetics of activation are normal in G-CSF sensitive t(8;21) AML cells.
AUTHOR(S): Da Silva, Nicolas; Meyer-Monard, Sandrine; Bastie, Jean-Noel; Dombret, Herve; Degos, Laurent; Chomienne, Christine
CORPORATE SOURCE: Lab. Biol. Cellulaire Hematopoietique, Inst. Hematologie, Hopital Saint-Louis, 1 ave. Claude-Vellefaux, 75475 Paris Cedex 10 France
SOURCE: Anticancer Research, (**Sept.-Oct., 1997**) Vol. 17, No. 5C, pp. 3961.
Meeting Info.: Seventh International Conference on Differentiation Therapy Versailles, France October 5-8, 1997
ISSN: 0250-7005.
DOCUMENT TYPE: Conference
LANGUAGE: English

L3 ANSWER 29 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:54161 BIOSIS
DOCUMENT NUMBER: PREV199799353364
TITLE: Lymphocytes from **patients** with chronic lymphocytic leukemia contain STAT1 and **STAT3** constitutively phosphorylated on serine.
AUTHOR(S): Mahajan, S.; Rudders, S. A.; Ritz, J.; Frank, D. A.
CORPORATE SOURCE: Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA USA
SOURCE: Blood, (1996) Vol. 88, No. 10 SUPPL. 1 PART 1-2, pp. 296A.

Meeting Info.: Thirty-eighth Annual Meeting of the American Society of Hematology Orlando, Florida, USA December 6-10, 1996.
ISSN: 0006-4971.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L3 ANSWER 30 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999004704 EMBASE
TITLE: Emerging applications of recombinant human granulocyte-macrophage colony-stimulating factor.
AUTHOR: Armitage J.O.
CORPORATE SOURCE: Dr. J.O. Armitage, University of Nebraska Medical Ctr., 600 S 42nd St, Omaha, NE 68198-3332, United States
SOURCE: Blood, (15 Dec 1998) 92/12 (4491-4508).
Refs: 187
ISSN: 0006-4971 CODEN: BLOOAW
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB rHuGM-CSF stimulates the proliferation and differentiation of multiple hematopoietic progenitor cells in the myeloid lineage and activates or augments many of the functional activities of mature neutrophils, monocytes/macrophages, and dendritic cells, enhancing host defenses against a broad spectrum of invading microorganisms. These properties have greatly expanded the possible therapeutic benefits of the cytokine in a wide variety of settings (Table 4), particularly those in which prevention of infection is desirable. The drug may be useful as prophylaxis or adjunctive treatment of bacterial or fungal infections in immunocompromised individuals, including cancer **patients** receiving myelosuppressive chemotherapy and **patients** with advanced HIV infection. In addition, exposure to rHuGM-CSF has recently been shown to reduce the susceptibility of macrophages to infection by HIV
Sargramostim is being evaluated as a vaccine adjuvant against infectious diseases and malignancies and as immunotherapy in the treatment of various malignancies, including melanoma and neuroblastoma. Based on the increasing variety of biologic effects being attributed to endogenous GM-CSF, additional clinical uses for sargramostim and molgramostim are under investigation. Because rHuGM-CSF has been shown to stimulate the migration and proliferation of endothelial cells and local application of rHuGM-CSF in animal studies has shown faster wound healing times, clinical trials have evaluated rHuGM-CSF in **patients** susceptible to mucosal damage, such as mucositis, stomatitis, and diarrhea, and those with nonhealing wounds and ulcers. It is likely that the future will see application of rHuGM-CSF in a variety of settings beyond those classically associated with myelosuppression.

L3 ANSWER 31 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998421613 EMBASE
TITLE: The regulation of heat shock proteins and their role in systemic lupus erythematosus.
AUTHOR: Stephanou A.; Latchman D.S.; Isenberg D.A.
CORPORATE SOURCE: Dr. D.S. Latchman, Centre fo Rheumatology, Bloomsbury Rheumatologic Unit, Arthur Stanley House, Tottenham St, London W1P 9PG, United Kingdom
SOURCE: Seminars in Arthritis and Rheumatism, (1998) 28/3 (155-162).
Refs: 54
ISSN: 0049-0172 CODEN: SAHRBF
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
031 Arthritis and Rheumatism
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objectives: After a serendipitous suggestion, it was established that a significant subset of **patients** with systemic lupus erythematosus (SLE) overexpress the 90-kD heat shock protein (Hsp90). In this review, we have analyzed our own data and that of others, to explore the link between Hsp90 and SLE. Methods: We performed a detailed literature review focusing on the potential role of Hsp in the etiopathogenesis of SLE. Results: Data are discussed showing surface expression of this Hsp in **patients** with lupus, a similar overexpression in the splenocytes of MRL/lpr mice before the onset of disease, the detection of antibodies to Hsp90 in a proportion of both lupus **patients** and lupus-prone mice, and most recently, an analysis of the transcription factors that regulate the production of this protein and the influence of key cytokines on these factors. Conclusions: These observations provide a model to show how a protein with key physiological roles in healthy individuals may, on occasion, become the target of an autoimmune attack with clinical consequences recognized in both mouse and human. Given that up to now, other heat shock proteins are not targeted in a similar fashion, the specificity of these responses is remarkable.

L3 ANSWER 32 OF 34 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1998:165268 SCISEARCH
THE GENUINE ARTICLE: YX516
TITLE: Oncostatin M and the interleukin-6 and soluble interleukin-6 receptor complex regulate alpha(1)-antichymotrypsin expression in human cortical astrocytes
AUTHOR: Kordula T; Rydel R E; Brigham E F; Horn F; Heinrich P C; Travis J (Reprint)
CORPORATE SOURCE: UNIV GEORGIA, DEPT BIOCHEM & MOL BIOL, LIFE SCI BLDG, ATHENS, GA 30602 (Reprint); UNIV GEORGIA, DEPT BIOCHEM & MOL BIOL, ATHENS, GA 30602; JAGIELLONIAN UNIV, INST MOL BIOL, PL-31120 KRAKOW, POLAND; ATHENA NEUROSCI INC, S SAN FRANCISCO, CA 94080; RHEIN WESTFAL TH AACHEN, INST BIOCHEM, D-5100 AACHEN, GERMANY
COUNTRY OF AUTHOR: USA; POLAND; GERMANY
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (**13 FEB 1998**) Vol. 273, No. 7, pp. 4112-4118.

Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 55

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB alpha(1)-Antichymotrypsin (ACT) is an acute phase protein expressed in the brain which specifically colocalizes with amyloid-beta during Alzheimer's disease, We analyzed ACT synthesis in cultured human cortical astrocytes in response to various cytokines and growth factors. Oncostatin M (OSM) and interleukin (IL)-1 beta were potent stimulators of ACT mRNA expression, whereas tumor necrosis factor-alpha had modest activity, and IL-6 and leukemia inhibitory factor (LIF) were ineffective. The finding that OSM, but not LIF or IL-6, stimulated ACT expression suggests that human astrocytes express a ''specific'' OSM receptor, but not IL-6 or LIF receptors, However, cotreatment of human, astrocytes with soluble IL-6 receptor (sIL-6R).IL-6 complex did result In potent stimulation of ACT expression. When the human ACT gene was cloned, two elements binding STAT1 and **STAT3** (signal transducer and activator of transcription) in response to OSM or IL-6.sIL-6R complexes could be identified and characterized, Taken together, these findings indicate that OSM or IL-6.sIL-6 complexes may regulate ACT expression in human astrocytes and thus directly or indirectly contribute to title pathogenesis of Alzheimer's disease.

L3 ANSWER 33 OF 34 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 96:887991 SCISEARCH
THE GENUINE ARTICLE: VT983
TITLE: Lymphocytes from **patients** with chronic lymphocytic leukemia contain STAT1 and **STAT3** constitutively phosphorylated on serine.
AUTHOR: Mahajan S (Reprint); Rudders S A; Ritz J; Frank D A
CORPORATE SOURCE: HARVARD UNIV, SCH MED, DANA FARBER CANC INST, BOSTON, MA 02115
COUNTRY OF AUTHOR: USA
SOURCE: BLOOD, (**15 NOV 1996**) Vol. 88, No. 10, Part 1, Supp. [1], pp. 1171-1171.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0006-4971.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L3 ANSWER 34 OF 34 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 96:573940 SCISEARCH
THE GENUINE ARTICLE: UZ454
TITLE: DISTINCT TUMORIGENIC POTENTIAL OF ABL AND RAF IN B-CELL NEOPLASIA - ABL ACTIVATES THE IL-6 SIGNALING PATHWAY
AUTHOR: HILBERT D M (Reprint); MIGONE T S; KOPF M; LEONARD W J; RUDIKOFF S
CORPORATE SOURCE: NCI, GENET LAB, NIH, BETHESDA, MD, 20892 (Reprint); NHLBI,
LAB MOL IMMUNOL, NIH, BETHESDA, MD, 20892; BASEL INST IMMUNOBIOL, CH-4005 BASEL, SWITZERLAND

COUNTRY OF AUTHOR: USA; SWITZERLAND
SOURCE: IMMUNITY, (**JUL 1996**) Vol. 5, No. 1, pp. 81-89.
ISSN: 1074-7613.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 77

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The development of murine plasma cell tumors induced by raf/myc containing retroviruses is facilitated by T cells and completely dependent on IL-6. To determine whether kinases with differing specificities reflect alternative biochemical pathways in B cell tumorigenesis, we have employed an abl/myc containing retrovirus to assess neoplastic development. In contrast with raf/myc, abl/myc disease is T cell and IL-6 independent. An examination of the IL-6 signal transduction pathway reveals that this pathway, as defined by activation of **Stat3**, is inducible by IL-6 in raf/myc tumors but constitutively activated in abl/myc tumors. These findings provide a mechanism for the derivation of cytokine-independent plasma cell tumors and suggest that both IL-6-dependent and independent tumors may arise in vivo depending on the particular mutational events incurred during tumorigenesis.